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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,814	07/26/2001	Madeline M. Butler	ISPH-0587	6393

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/915,814	BUTLER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15 and 72-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15 and 72-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 7-1-04 and 9-2-04.

Claims 1, 2, 4-15 and 72-83 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-2-04 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn. Applicants' arguments are addressed as they pertain to the instant rejections set forth below.

Maintained Rejections

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of human hormone sensitive lipase (hsl) of SEQ ID NO: 3 comprising the administration of antisense oligonucleotides that target and specifically inhibit the expression of SEQ ID NO: 3, and being enabling

for the in vivo targeting and inhibition of hsl expression (of SEQ ID NO: 3) in the liver of mice, for the decrease in liver weight in mice, for the decrease in serum insulin levels of male ob/ob mice, and for a decrease in serum cholesterol and triglycerides in male ob/ob mice and in P-407 hyperlipidemia model mice following the intraperitoneal administration of the antisense oligonucleotide of SEQ ID NO: 179, does not reasonably provide enablement for the in vivo inhibition of hsl comprising the administration of any antisense and further whereby treatment effects are provided in an animal, for the same reasons of record set forth in the Office action mailed 1-14-03.

Applicant's arguments filed 7-1-04 have been fully considered but they are not persuasive. Applicants argue that the full scope of the claim is enabled because the instant application teaches that administration of antisense provides specific biological responses. Applicants are correct that the administration of SEQ ID NO: 179 produces specific biological responses, as delineated in the above paragraph (e.g. regarding serum cholesterol levels, inhibition of expression of the HSL target gene). But, contrary to Applicants' assertions, the teaching of target gene inhibition and treatment effects provided upon administration of the antisense of SEQ ID NO: 179 is not representative of the ability to successfully target and inhibit the expression of hsl in vivo using any antisense oligonucleotide. The adequate delivery of a particular antisense molecule to an appropriate target cell, whereby it hybridizes to the corresponding region of the target gene and inhibits its expression in vivo, depends on various factors, including accessibility of the corresponding target region to the antisense molecule (which depends on various factors, including higher order structure of the target gene and

antisense accessibility). The success of one antisense molecule to achieve adequate uptake, target binding and inhibition therefore, is not predictive of a distinct and different antisense, targeting a different region of the gene, to do the same. Therefore it would require undue experimentation beyond the examples provided for the single antisense of SEQ ID NO: 179, whereby other antisense target and inhibit expression of HSL of SEQ ID NO: 3 in vivo.

New Rejections and Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 72-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to antisense oligonucleotide compounds that inhibit the expression of hsl of SEQ ID NO: 3 by at least 15, 40, 50 or 60% in 80% confluent HepG2 cells in culture at an optimal compound concentration. The specification and claims do not indicate which antisense oligonucleotides inhibit the expression of hsl of SEQ ID NO: 3 by 15, 40, 50 or 60% in 80% confluent HepG2 cells (e.g. there is no

support for all of these increments of inhibition for the various antisense claimed). These limitations therefore constitute new matter. The instant specification on pages 76-77 generally describes procedures that can be used to determine the optimal concentration of an antisense oligonucleotide in inhibiting the expression of the target hsl gene of SEQ ID NO: 3 in a target cell in culture. The specification also provides Table 2 on pages 89-90, which lists various and particular antisense oligonucleotides, and the extent of inhibition of SEQ ID NO: 3 expression that was achieved at an unspecified concentration, in an unspecified target cell in vitro. The specification fails to adequately describe, however, the oligonucleotide sequences and optimal concentrations that provide for the levels of inhibition claimed, and in 80% confluent HepG2 target cells. The scope of the claims includes structural variants (e.g. particular sequences that achieve a particular extent of inhibition in a particular target cell population at a particular density in vitro) and a significant number of differences between members of this broad genus is permitted. Concise features that could distinguish members within the genus from others are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. And because the genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide an adequate description of the genus claimed. Thus, Applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 11-14, 76-80 are rejected under 35 U.S.C. 102(a) as being anticipated by Mitchell et al.

Mitchell et al (WO 01/26664, document "AA" provided in the IDS, filed October 19, 2001) teach compositions comprising oligonucleotide mimetic compounds between 8-50 nucleobases which specifically target an active site on and inhibit the expression of hsl of SEQ ID NO: 3 in vitro, and which compounds comprise antisense oligonucleotides comprising phosphorothioate internucleotide linkages, 2'-O methoxyethyl modified sugars, and which compositions further comprise a pharmaceutically acceptable carrier and a colloidal dispersion system (See entire document, especially page 4, line 1-page 8, line 4, page 11, line 20-page 13, line 31 and the sequence alignment data provided in the Office action mailed 1-14-03).

Applicant's arguments filed 7-1-04 have been fully considered but they are not persuasive. Applicants argue that Mitchell is not anticipatory because it lacks disclosure of the class of compounds having the specifically recited length of 8 to 50 nucleobases and fails to disclose a specific example of a compound of this range. Contrary to Applicants' assertions, Mitchell describes mimetic antisense oligonucleotides for targeting and inhibiting the expression of hsl, which antisense oligonucleotides "may comprise from 5 to about 100 nucleotide units." (See page 8, lines 1-2 of Mitchell). This

range encompasses the instantly claimed compounds, which claims are drawn to antisense oligonucleotides between 8-50 nucleobases in length targeted to a nucleic acid molecule encoding HSL, and hence properly anticipates the instantly claimed invention. Applicants also argue that Mitchell fails to disclose any specific antisense compounds, much less any that actually inhibit expression of hsl to any degree in any cell type. It must be pointed out, however, that the instant claims which are anticipated by Mitchell are not drawn to any specific antisense compounds, nor are they drawn to antisense that inhibit expression to any degree in a cell type. In addition, Applicant is reminded that, in the case where prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products (i.e. those describe by Mitchell) do not necessarily or inherently possess the characteristics of his claimed product.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented

and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 11, 12, 14 and 72-75 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Holly et al.

Holly et al (USPN 5,502,034) teach an antisense oligonucleotide between 8-50 nucleobases that specifically hybridizes with nucleotides 1143-3775 of SEQ ID NO: 3, encoding human hormone sensitive lipase (hHSL) and inhibits its expression in vitro (see SEQ ID NO: 5 of Holly, and the accompanying sequence alignment data, which is attached to the Office action).

The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re

Best 195 USPQ 430 as per above. The sequence cited above that shares less than 100% homology with the target gene (see accompanying alignment data illustrating 85% homology) is presumed to have inhibitory function since sequences with less than 100% homology meet the structural requirements of the claimed invention as indicated in the instant specification under the discussion of "specifically hybridizing." (e.g. page 9, line 9-page 10, line 6 of the instant specification). Therefore, absent evidence to the contrary, since the oligonucleotide disclosed by Holly et al meets all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically inhibiting expression hHSL in HepG2 cells in vitro as claimed.

Therefore, absent evidence to the contrary, claims 1, 2, 11, 12, 14 and 72-75 are anticipated by or, in the alternative, obvious over Holly et al.

Claims 1, 2, 11, 12, 14 and 72-75 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Strosberg et al.

Strosberg et al (WO 96/34100) teach an antisense oligonucleotide between 8-50 nucleobases that specifically hybridizes with nucleotides 1143-3775 of SEQ ID NO: 3, encoding human hormone sensitive lipase (hHSL) and inhibits its expression in vitro (see Accession No. AAT43117, example 1 on p. 17 and the accompanying sequence alignment data, which is attached to the Office action).

The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotide disclosed by Strosberg et al meets all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically inhibiting expression hHSL in vitro.

Therefore, absent evidence to the contrary, claims 1, 2, 11, 12, 14 and 72-75 are anticipated by or, in the alternative, obvious over Strosberg et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-15 and 72-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitchell and Strosberg et al as applied to claims 1, 2, 11-14 and 72-80 above, in view of Langin and Holst, the combination in view of Milner et al and McKay, the combination in view of Laurell et al and Kosaki et al insofar as the claims are drawn to compositions and methods comprising the administration of antisense oligonucleotides between 8 and 50 nucleobases in length that specifically target hHSL of SEQ ID NO: 3 (and including those antisense oligonucleotides that specifically target the region of nucleotides 1-970 or 1143-3775 of SEQ ID NO: 3) and inhibit hsl expression (e.g. by at least 5, 15, 40, 50 or 60%) in 80% confluent HepG2 cells in culture, and which antisense comprise phosphorothioate internucleotide linkages, 2'-O-

methoxyethyl sugar moieties, 5-methylcytosine, or which antisense are optionally chimeric, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Mitchell and Strosberg are relied upon as cited in the 102/103 rejections above.

Holst et al (Holst, L. S. et al, Genomics 35: 441-447, 1996) teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3. Holst et al also teach hsl as an important regulator of energy homeostasis, which is poorly understood (See the first paragraph on p. 441, and the fourth full paragraph on p. 442).

Langin et al (Langin, D. et al., Proc. Natl. Acad. Sci, USA, 90: 4897-4901, 1993) teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3. Langin et al also teach the possible role of hsl in pathophysiological states including obesity and diabetes as a motivation to study this molecule (See second full paragraph in right hand column on p. 4897, second and fourth full paragraphs on p. 4898; see also Accession No. 711706, deposited by Langin et al to Genbank, encoding hsl).

The primary references of Mitchell, Strosberg, Holst ad Langin do not teach the inhibition of hsl expression in HepG2 cells in vitro, nor the incorporation of 5-methyl cytosine (modified nucleobase) residues, nor the incorporation of chimeric structures into antisense oligonucleotides.

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the

expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which compositions further comprise a colloidal dispersion system and a pharmaceutically acceptable carrier. McKay et al also teach the in vitro inhibition of various antisense oligonucleotides between 8-50 nucleobases that specifically hybridize with the target gene (see especially col. 6, line 29 through col. 15, line 10; col. 20, line 18 through col. 24, line 67; see also Tables 2 and 3 in col. 37-38).

Laurell et al (Biochem. J., 328: 137-143, 1997) teach that hsl catalyzes the rate limiting step of adipose tissue lipolysis, and that hsl is a critical enzyme in fat and energy accumulation in the body (first paragraph of the introduction, p. 137). Laurell et al teach the ability of insulin to antagonize hormone induced lipolysis by decreasing cAMP levels and activating phosphodiesterases (first paragraph of the introduction, p. 137). Laurell et al additionally teach the regulation of hsl via its phosphorylation (*id.*) and that hsl is under hormonal regulation (*id.*).

Kosaki et al (J. Biol. Chem., 270(35): 20,816-20,823, 1995) teach the use of HepG2 cells as a model cell line because it is one of the major sites of insulin action (second paragraph of the introduction on page 20,816). Kosaki et al also teach the B

isoform of insulin to have greater insulin stimulated kinase activity (last paragraph on page 20,823).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of hsl of SEQ ID NO: 3 in vitro, because Milner et al and McKay teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro using routine screening assays that are well known in the art (see Milner at pages 539-540 and McKay at col. 6-15). In addition, Mitchell and Langin et al teach the nucleotide sequence of the target hsl gene and Strosberg et al teach antisense that specifically target hsl between nucleotides 1143-3775 of SEQ ID NO: 3, and inhibit the in vitro expression of hsl of SEQ ID NO: 3. One of ordinary skill in the art would have been motivated to inhibit the expression of HSL in vitro to study its role in diabetes and obesity, as taught by Langin, and to study the effect on lipolysis because this enzyme is known to catalyze the rate limiting step in adipose lipolysis, and is critical in fat and energy accumulation in the body, as taught previously by Laurell et al. One of ordinary skill in the art would have been motivated to inhibit hsl expression using antisense in HepG2 cells in vitro because HepG2 cells have been utilized historically to study the effects of insulin action on various aspects of cellular metabolism, and these cells therefore are appropriate to study the involvement of insulin in regulating HSL, and to study the effects of insulin on the process of lipolysis (e.g. when HSL expression is inhibited in such model cells). It would have been obvious to one of ordinary skill in the art to inhibit the expression of the hsl nucleic acid of known

nucleotide sequence (e.g. SEQ ID NO: 3) in vitro using antisense oligonucleotides because the methods for inhibiting a target gene of known sequence using antisense had been taught previously by Milner et al and such methods of screening antisense in vitro for inhibition of target gene expression were routine at the time the invention was made. Milner et al additionally teach methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. McKay et al also teach the routine screening of specific antisense oligonucleotides for their ability to inhibit the expression of their corresponding target gene in vitro. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, and also taught by McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides (between 8-50 nucleobases) for the in vitro inhibition of hsl expression of SEQ ID NO: 3. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by Mitchell and McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary skill in the art would have been motivated to utilize pharmaceutically acceptable diluents in order to achieve the appropriate concentration of antisense oligonucleotides for administration to target cells in a manner which is compatible for maintaining cellular

integrity and antisense stability and one would have been motivated to utilize colloidal dispersions in order to enhance antisense stability and cellular delivery of antisense, as taught by McKay et al. One of ordinary skill in the art would have expected that the delivery of modified antisense (mimetics) to target cells harboring hsl, including HepG2 cells, which antisense specifically hybridize with the target nucleic acid encoding hsl (i.e. of SEQ ID NO: 3), would lead to inhibition of expression of hsl in vitro.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Applicant's arguments filed 7-1-04 have been fully considered but they are not persuasive. Applicants argue that Langin and Holst disclose antisense oligonucleotides between 8 and 50 nucleobases, but fail to disclose hybridization conditions or specific sequences and so cannot be expected to inhibit hsl expression to any degree in any cell type. Applicants also suggest that extreme conditions can be used to force almost any two single stranded nucleic acids to hybridize regardless of sequence complimentarily and therefore no assumption can be made about the antisense oligonucleotides disclosed by Langin and Holst regarding their ability to specifically target and inhibit hsl expression to any degree in HepG2 cells in vitro. Contrary to Applicants' assertions, Holst teaches an antisense oligonucleotide that specifically hybridized to the target hsl nucleic acid under "standard conditions" (see 4th full paragraph on page 442 of Holst). Langin teach a 21 nucleobase antisense oligonucleotide that hybridized to the target hsl nucleic acid at 42°C, and under conditions conducive for enzymatic reverse transcription. (see last paragraph on the left on page 4898 of Langin.) These conditions

utilized by either Langin or Holst are not extreme conditions as suggested by Applicant, but instead are conditions under which an oligonucleotide which is complementary to a target nucleic acid would be reasonably expected to specifically hybridize and inhibit transcription.

Applicants argue that the worker of ordinary skill would have no reason to consider the disclosures of either Holst or Langin in an obviousness rejection because these references relate to cloning and nothing more. Contrary to Applicants' assertions, the antisense oligonucleotides relied upon by Holst or Langin were used because of their ability to specifically hybridize with the target hsl nucleic acid and so are pertinent because they teach antisense oligonucleotides which are claimed in the instant invention (albeit without any stabilizing modifications). Moreover, the primary sequence of hsl, its genetic organization and its biological relevance (e.g. its critical role in energy homeostasis as an enzyme that catalyzes the release of free fatty acids for transport as energy sources to energy requiring tissues) are taught by Holst and Langin, all of which are relevant and crucial for the motivation and means of targeting hsl for inhibition by antisense oligonucleotides.

Applicants also argue that the instant invention is not obvious over the references of Mitchell and Milner because Mitchell provides no working examples of antisense that inhibit the target hsl and inhibit its activity, while Milner teaches a single oligonucleotide from an array of oligonucleotides tested that successfully targets and inhibits both alpha and beta globin synthesis. Contrary to Applicants' assertions, Mitchell teaches antisense oligonucleotides between 8-50 nucleobases in length that specifically target

and inhibit the expression of hsl in vitro. This disclosure, combined with the teachings of Milner in disclosing the routine empirical screening of antisense for their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537). Applicants assert that an extremely low demonstration of success for identifying antisense compounds that would inhibit target polynucleotides is demonstrated in the teachings of Milner and therefore the combination of references do not render the instant invention obvious. Contrary to applicants' assertions, the combinatorial technique taught by Milner allows for a simultaneous assessment of all possible oligonucleotides within a given region to inhibit target nucleic acid expression. The lack of correlation of predicted secondary mRNA structure with successful antisense inhibition was brought to light by the teachings of Milner, but this lack of correlation does not make the routine screening method for finding effective inhibitory antisense any less routine, it simply warns that one cannot design antisense based simply on secondary structural predications. The routine use of antisense oligonucleotides for inhibiting target gene expression render the instant invention obvious to one of ordinary skill in the art of molecular biology (see Milner at 537, who teaches a combinatorial technique that allows simultaneous assessment of all possible oligonucleotides within a given region to identify sequences open to duplex formation and antisense inhibition of target gene expression: "...the arrays provide a simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence.").

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JZ
11-11-04

TC1600